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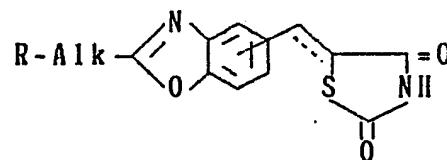
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⑳ Benzoxazole derivatives and preparation thereof.

㉑ Novel benzoxazole derivative of the formula:



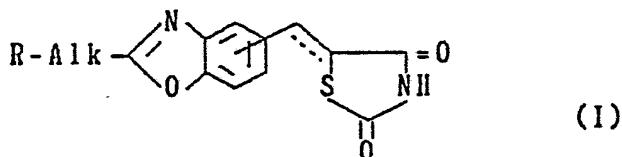
wherein R is a substituted or unsubstituted phenyl group, a substituted or unsubstituted naphthyl group, a substituted or unsubstituted cycloalkyl group or a substituted or unsubstituted heterocyclic group; Alk is single bond, a substituted or unsubstituted lower alkylene group, a lower alkenylene group or a lower alkynylene group; the group is a group of the formula: -CH<sub>2</sub>- or -CH=, and a pharmaceutically acceptable salt thereof are disclosed. Said derivative (I) and a salt thereof are useful as therapeutic agents for diabetes.

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Benzoxazole derivatives and preparation thereof

This invention relates to a novel benzoxazole derivative, and processes for preparing same. More particularly, it relates to a benzoxazole derivative of the formula:

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wherein R is a substituted or unsubstituted phenyl group, a substituted or unsubstituted naphthyl group, a substituted or unsubstituted cycloalkyl group or a substituted or unsubstituted heterocyclic group; Alk is single bond, a substituted or unsubstituted lower alkylene group, a lower alkenylene group or a lower alkynylene group; and the group  $\text{Alk}$  is a group of the formula:  $-\text{CH}_2-$  or  $-\text{CH}=\text{}$ , or a pharmaceutically acceptable salt thereof.

A variety of biguanide derivatives and sulfonylurea derivatives have been so far used for treatment of diabetes. However, these anti-diabetic agents are still unsatisfactory in that the biguanide and sulfonylurea derivatives cause side effects such as lactic acidosis and severe hypoglycemia, respectively.

20 The novel benzoxazole derivative (I) of the present invention and a salt thereof are useful for therapeutic treatment of diabetes because they elevate insulin sensitivity and show potent hypoglycemic activity.

Examples of the benzoxazole derivative of the present invention are those of the formula (I) in which R is phenyl group, naphthyl group, cyclohexyl group, 1,3-thiazol-4-yl group, 1,3-oxazol-4-yl group, pyridyl group, benzoxazolyl group, thienyl group, quinolyl group or benzofuranyl group [these groups may 25 optionally have a substituent or substituents selected from a (lower alkoxy)carbonyl group, a lower alkoxy group, a lower alkyl group, a trihalogeno-lower alkyl group, a lower alkylthio group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, phenyl group, phenoxy group, a phenyl-lower alkoxy group, hydroxy group, a halogen atom, nitro group, amino group, a lower alkanoylamino group, a di(lower alkyl)amino group, a cycloalkyl group, pyrrolidino group, piperidino group, morphorino group and pyrrolyl group.]; and 30 Alk is single bond, a straight or branched lower alkylene group, a lower alkenylene group or a lower alkynylene group [said lower alkylene group may optionally be substituted with hydroxy group, oxygen atom, phenyl group or a cycloalkyl group].

Among them, preferred examples of the benzoxazole derivative of the invention are those of the formula (I) in which R is ① a phenyl group which may optionally have 1 to 3 substituent(s) selected from the 35 above mentioned groups; ② a naphthyl group which may optionally be substituted with a lower alkoxy group, a lower alkyl group, a halogen atom or nitro group; ③ a cyclohexyl or pyridyl group which may optionally be substituted with a lower alkyl group; ④ a 1,3-thiazol-4-yl or 1,3-oxazol-4-yl group which may 40 optionally have 1 to 2 substituent(s) selected from a lower alkyl group, a lower alkylthio group, a cycloalkyl group and phenyl group; ⑤ a 1,3-benzoxazolyl group which may optionally be substituted with phenyl group; ⑥ thienyl group; ⑦ quinolyl group; or ⑧ benzofuranyl group.

More preferred examples of the compound of the invention are those of the formula (I) in which R is 1 ① a phenyl group which may optionally have 1 to 3 substituent(s) selected from a lower alkoxy group, a lower alkyl group, a trihalogeno-lower alkyl group, a lower alkylthio group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, phenyl group, a halogen atom, nitro group, pyrrolidino group, piperidino group, 45 morphorino group, pyrrolyl group and a di(lower alkyl)amino group; ② a naphthyl group which may optionally be substituted with a lower alkoxy group, a lower alkyl group, a halogen atom or nitro group; ③ a pyridyl group which may optionally be substituted with a lower alkyl group; or ④ a 1,3-thiazol-4-yl or 1,3-oxazol-4-yl group which may 50 optionally have 1 to 2 substituent(s) selected from a lower alkyl group, a lower alkylthio group, a cycloalkyl group and phenyl group.

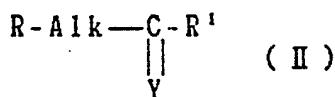
Other preferred examples of the benzoxazole derivative of the invention are those of the formula (I) in which Alk is a straight or branched lower alkylene group and/or 2,4-dioxothiazolidin-5-yl(or ylidene)-methyl group is bound to the benzoxazole ring at the 5- or 6-position thereof, especially at the 5-position thereof.

In the above-mentioned examples of the benzoxazole derivative (I), the lower alkoxy group, the lower alkyl group, the lower alkanoyl group, the cycloalkyl group, the lower alkylene group, the lower alkenylene

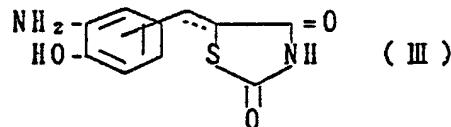
group and the lower alkynylene group include an alkoxy group of one to six carbon atoms, an alkyl group of one to six carbon atoms, an alkanoyl group of two to six carbon atoms, a cycloalkyl group of three to nine carbon atoms, an alkylene group of one to four carbon atoms, an alkynylene group of two to four carbon atoms and an alkynylene group of two to four carbon atoms, respectively. Preferred examples of these 5 group are an alkyl group of one to four carbon atoms, an alkenyl, alkynyl or alkanoyl group of two to five carbon atoms, and a cycloalkyl group of four to seven carbon atoms.

On the other hand, the benzoxazole derivatives (I) of the present invention in which the 2,4-dioxothiazolidine binds to the benzoxazole ring via methylene group (i.e., the compound in which the group  $\text{---CH}_2\text{---}$  is methylene group) may exist in the form of two optically active isomers due to the 10 asymmetric carbon atom thereof. On the other hand, the benzoxazole derivative (I) of the present invention in which the 2,4-dioxothiazolidine binds to benzoxazole ring via a group of the formula:  $-\text{CH}=\text{}$  (i.e., the compound in which the group  $\text{---CH}=\text{}$  is  $-\text{CH}=\text{}$ ) may exist in the form of the two geometrical isomers. The present invention includes within its scope either one of these optical or geometrical isomers and a mixture thereof.

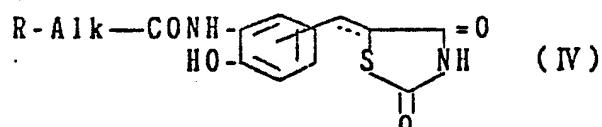
15 According to the present invention, the compound (I) can be prepared by the step of:  
(1) condensing a compound of the formula:



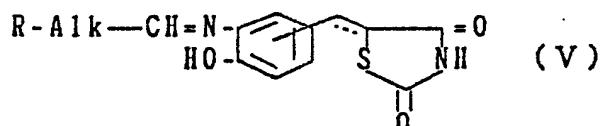
wherein R' is hydroxy group, a lower alkoxy group or a reactive residue, Y is oxygen atom or imino group, and R and Alk are the same as defined above, or a salt thereof with a dioxothiazolidine compound of the 25 formula:



wherein the symbol is the same as defined above, or a salt thereof,  
35 (2) dehydrating an amide of the formula:

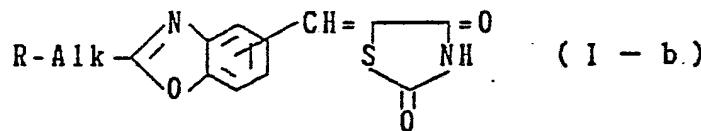


wherein the symbols are the same as defined above, or a salt thereof, or  
45 (3) dehydrogenating an azomethine compound of the formula:



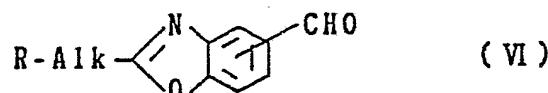
wherein the symbols are the same as defined above, or a salt thereof.  
Among the compound (I) of the invention, an olefinic compound of the formula:  
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wherein the symbols are the same as defined above, may also be prepared by reacting an aldehyde compound of the formula:

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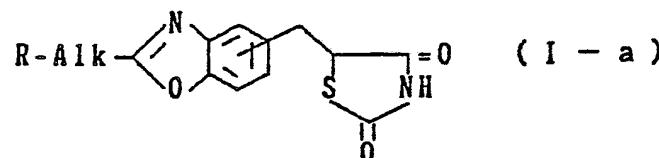


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wherein the symbols are the same as defined above, or a salt thereof with 2,4-dioxothiazolidine or a salt thereof.

On the other hand, the compound of the formula:

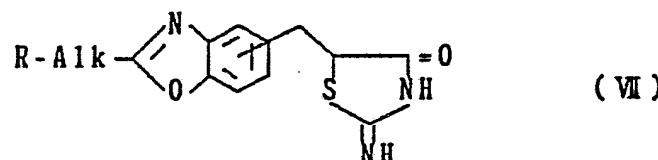
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wherein the symbols are the same as defined above, may be prepared by hydrolysis of an imino compound of the formula:

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wherein the symbols are the same as defined above, or a salt thereof or reduction of the compound (I-b) or a salt thereof.

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The starting compound (II) in which Y is oxygen atom, and the starting compound (III) to (V) and (VII), compound (I-b) and 2,4-dioxothiazolidine, may, if required, be used for the above reactions in the form of a mineral acid salt (e.g., hydrochloride), an alkali metal salt, an alkaline earth metal salt. The starting compound (II) in which Y is imino group and the starting compound (VI) may, if required, be used for the above reaction in the form of a salt with a mineral acid (e.g., hydrochloric acid).

45

When the group Y is oxygen atom, the condensation of the starting compound (II) or a salt thereof and the dioxothiazolidine compound (III) or a salt thereof can be conducted in the presence or absence of a condensing agent. Preferred examples of the reactive residue (R<sup>1</sup>) include halogen atoms such as chlorine or bromine atoms. Trimethylsilyl polyphosphate, ethyl polyphosphate and the like are preferably used as the condensing agent. If required, the reaction may be carried out in an inert solvent such as dichlorobenzene, dichloromethane, tetrahydrofuran, benzene or toluene. On the other hand, when the group Y is imino group, the condensation of the starting compound (II) or a salt thereof and the compound (III) can be conducted in a solvent. Dioxane, tetrahydrofuran, ethanol or methanol are suitable as the solvent. Either one of these reactions may be carried out at 40 to 260 °C.

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The dehydration of the amide (IV) or a salt thereof can be conducted in the presence or absence of a dehydrating agent or an acid. It is preferred to carry out the reaction in an inert solvent such as those mentioned above; but, if the reaction is carried out in the absence of the dehydrating agent or an acid, it is not always necessary to use a solvent. Preferred examples of the dehydrating agent and acid include

phosphoryl chloride, thionyl chloride, trimethylsilyl polyphosphate, ethyl polyphosphate, p-toluenesulfonic acid and the like. It is preferred to carry out the reaction at 50 to 250 °C.

The dehydrogenation of the azomethine compound (V) or a salt thereof can be conducted in the presence of a dehydrogenating agent. Examples of such dehydrogenating agent include lead tetraacetate, 6 nickel peroxide and the like. It is preferred to carry out the reaction at 0 to 100 °C in a solvent such as dioxane, tetrahydrofuran, benzene, toluene, water, ethyl acetate, acetic acid, pyridine and the mixture thereof.

The reaction of aldehyde compound (VI) or a salt thereof and 2,4-dioxothiazolidine or a salt thereof can be conducted in the presence or absence of a base. Piperidine, pyridine, a tri(lower alkyl)amine, sodium 10 hydride, sodium methylate, sodium ethylate, lithium diisopropyl amide, etc., can be used as a base. The solvent which is used in the condensation of the compound (II) in which Y is imino group can be used in this reaction. It is preferred to carry it out at 0 to 150 °C.

Hydrolysis of the imino compound (VII) or a salt thereof can be conducted in an inert solvent according to a conventional manner. For example, said hydrolysis is preferably carried out by treating the compound 15 (VII) with an acid such as hydrochloric acid, hydrobromic acid, hydroiodic acid, p-toluenesulfonic acid, trifluoroacetic acid, methanesulfonic acid and the like. It is also preferred to carry it out at 50 to 150 °C. On the other hand, reduction of olefinic compound (I-b) or a salt thereof can be conducted in the presence of a catalyst in hydrogen atmosphere. Palladium carbon, palladium, platinum oxide or Raney nickel can be 20 used as a catalyst. It is preferred to carry it out at 10 to 80 °C. In these hydrolysis and reduction, dioxane, tetrahydrofuran, ethanol, methanol, ethylene glycol monomethyl ether, acetic acid and the mixture thereof are suitable as the solvent.

Concomitantly, the benzoxazole derivative (I) of the invention in which Alk is a lower alkylene group substituted with oxo group may be converted into the corresponding benzoxazole derivative (I) in which Alk is a hydroxy-lower alkylene group. This conversion is carried out by reduction of the former derivative with 25 a reducing agent such as sodium borohydride at 0 to 100 °C in an inert solvent such as methanol, ethanol, tetrahydrofuran and the mixture thereof. On the other hand, the benzoxazole derivative (I) in which R is a lower alkylsulfinyl- or lower alkylsulfonylphenyl group may be obtained by oxidation of the benzoxazole derivative (I) in which R is a lower alkylthiophenyl group. Said oxidation is preferably carried out by treatment with an oxidative agent such as m-chloroperbenzoic acid, perbenzoic acid or peracetic acid at -70 30 to 100 °C in an inert solvent such as lower alkanol, methylene chloride, chloroform, tetrahydrofuran, dioxane, water and the mixture thereof. Alternatively, the benzoxazole derivative (I) in which R is a hydroxyphenyl group may be obtained by debenzylation of the benzoxazole derivative (I) in which R is a benzyloxyphenyl group. Said debenzylation is preferably carried out by treatment with an acid such as hydrochloric acid or hydrobromic acid at 0 to 100 °C in an inert solvent such as acetic acid.

35 The benzoxazole derivative (I) of the present invention and a salt thereof exhibit potent hypoglycemic activity and are useful for treatment and/or prophylaxis of diabetes, especially for the treatment of patients with non-insulin dependent diabetes. Such therapeutic effect of the compound (I) is based on the elevation of insulin sensitivity in cells and, unlike the known anti-diabetic agents, said compound is advantageous in that it can be used as an anti-diabetic agent without affecting patients of normal blood glucose level. 40 Moreover, the toxicity of the benzoxazole derivative (I) of the present invention is low. For example, when 5-[(2,4-dioxothiazolidin-5-yl)methyl]-2-[(2-phenylthiazol-4-yl)methyl]benzoxazole at a dose of 100 mg/kg (CMC suspension) was orally administered to mice, no mice died during a 72 hour-observation period.

The benzoxazole derivative (I) can be used for pharmaceutical use either in the free form or in the form 45 of a salt. Suitable salts of the compound (I) for pharmaceutical use include, for example, pharmaceutically acceptable salts such as an alkali metal salt (e.g., sodium salt, potassium salt), an alkaline earth metal salt (e.g., calcium salt, magnesium salt), and acid addition salts (hydrochloride or sulfate). Such salt may be obtained by treating the compound (I) with a stoichiometrically equimolar amount of the acid or base according to a conventional manner.

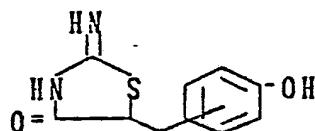
50 The compound (I) and a salt thereof may be administered either orally or parenterally and may also be used in the form of a pharmaceutical preparation containing the same compound in admixture with pharmaceutical excipients suitable for oral or parenteral administration. The pharmaceutical preparations may be in solid form such as tablets, capsules or suppositories or in liquid form such as solutions, suspensions or emulsions. Moreover, when administered parenterally, the pharmaceutical preparation may be used in the form of injections.

55 The dose of the compound (I) or a salt thereof may vary depending on the age, condition and body weight of patients, the kind and severity of diseases to be treated and administration route, etc, but may usually be about 0.005 to about 100 mg/kg, preferably about 0.01 to about 10 mg/kg, per day.

All of the starting compounds (III) to (VII) of the invention are novel. Among them, the dioxothiazolidine

compound (III) in which the group  is methylene group can be prepared by hydrolyzing a compound of the formula:

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and then nitrating the product with conc. nitric acid, followed by reduction with a reducing agent such as sodium hypophosphite in the presence of a catalyst such as palladium-carbon at 0 to 100 °C. On the other hand, the dioxothiazolidine compound (III) in which the group  is a group of the formula: -CH= can be prepared by condensing 4-hydroxy-3-nitrobenzaldehyde or 3-hydroxy-4-nitrobenzaldehyde with 2,4-dioxothiazolidine in the presence of a base (e.g., piperidine), and then treating the product with a reducing agent (e.g., sodium hypophosphite) in the presence of a catalyst (e.g., palladium carbon). The amide (IV) can be prepared by condensing the dioxothiazolidine compound (III) and the compound (II) under a mild condition, e.g., in the presence of a condensing agent such as dicyclohexylcarbodiimide. The azomethine compound (V) can be prepared by condensing the compound of the formula:

15

R-Alk-CHO

wherein the symbols are the same as defined above, or a salt thereof with the dioxothiazolidine compound (III) in the presence or absence of a catalyst (e.g., hydrochloric acid). Aldehyde compound (VI) can be prepared by dehydrating the compound of the formula:

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wherein the symbols are the same as defined above, or a salt thereof according to the same condition of the dehydration of the compound (IV). Further, the imino compound (VI) or a salt thereof can be prepared by diazotizing the aniline compound of the formula:

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wherein the symbols are the same as defined above, or a salt thereof in the presence of hydrogen halide, reacting the product with methyl acrylate in the presence of a copper catalyst (e.g., copper(I) oxide), and then reacting the product with thiourea in the presence of a base such as sodium acetate.

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Experiment

Genetically obese and diabetic mice, KK-A<sup>y</sup> (Tokyo Laboratory Animals Science Corp., Tokyo, Japan; 1.5 to 11 months old), were used. Mice were divided into groups of 4 mice with roughly equal means in blood glucose level and body weight after prefeeding powdered chow (CE-2, Clea Japan Inc., Tokyo, Japan). Mice were fed ad libitum for 5 days the powdered chow containing 0.5 mg% of test compound. After 5 days, blood was collected from the tail tip. Blood glucose was enzymatically determined. Hypoglycemic activity of test compound was calculated as follows:

$$55 \quad \text{blood glucose level of the medicated group} \quad \times 100 \\ \times 1 - \frac{\text{blood glucose level of the non-medicated group}}{\text{blood glucose level of the medicated group}}$$

The results are shown in Table 1.

Table 1

Test compounds	Hypoglycemic activity
5-((2,4-dioxothiazolidin-5-yl)methyl)-2-((2-phenylthiazol-4-yl)methyl)benzoxazole	63%
5-((2,4-dioxothiazolidin-5-yl)methyl)-2-((2-phenyloxazol-4-yl)methyl)benzoxazole	52%
5-((2,4-dioxothiazolidin-5-yl)methyl)-2-((5-methyl-2-cyclohexyloxazol-4-yl)methyl)benzoxazole	49%
5-((2,4-dioxothiazolidin-5-yl)methyl)-2-((5-methyl-2-phenyloxazol-4-yl)methyl)benzoxazole	58%

Example 1

(1) A mixture of 1.76 g of sodium nitrite in 5 ml of water is added dropwise under ice-cooling to a mixture of 4.87 g of 5-amino-2-phenylbenzoxazole, 6 ml of conc. hydrochloric acid and 50 ml of acetone. The mixture is stirred at the same temperature for 10 minutes, and then 12.1 g of methyl acrylate are added thereto. 150 mg of copper(II) oxide are added gradually to the mixture at 40 °C. After nitrogen gas evolution ceases, the mixture is kept at 35 °C for 20 minutes. Water is added thereto, and the aqueous mixture is extracted with ethyl acetate. The extract is washed with water, dried and evaporated to remove the solvent. The residue is purified by silica gel column chromatography (solvent; chloroform), whereby 5.13 g of methyl 3-(2-phenylbenzoxazol-5-yl)-2-chloropropionate are obtained as pale brown oil. IR  
 $\nu$  Neat max (cm<sup>-1</sup>): 1740

55 (2) A mixture of 5.13 g of the product obtained above, 2.30 g of thiourea, 1.50 g of sodium acetate and 35 ml of ethylene glycol monomethyl ether is heated at 100 °C for 8 hours. The solvent is distilled off, and water and n-hexane are added to the residue. The precipitated crystals are collected by filtration, washed, and dried, whereby 4.35 g of 5-[(2-imino-4-oxothiazolidin-5-yl)methyl]-2-phenylbenzoxazole are obtained as colorless powder. M.p. 281 to 283 °C (decomp.)

(3) 3.18 g of the product obtained above are dissolved in 50 ml of ethylene glycol monomethyl ether, and 2.05 g of toluenesulfonic acid monohydrate and 6 ml of water are added thereto. After the mixture is refluxed for 1 hour and 45 minutes, the solvent is distilled off. Water is added to the residue, and the solution is extracted with ethyl acetate. The extract is washed, dried, and evaporated to remove the solvent.

5 The residue is purified by silica gel column chromatography (solvent; chloroform : methanol = 20 : 1), whereby 1.83 g of 5-[(2,4-dioxothiazolidin-5-yl)methyl]-2-phenylbenzoxazole are obtained.

M.p. 192 to 194 °C

Mass(m/e):324(M<sup>+</sup>)

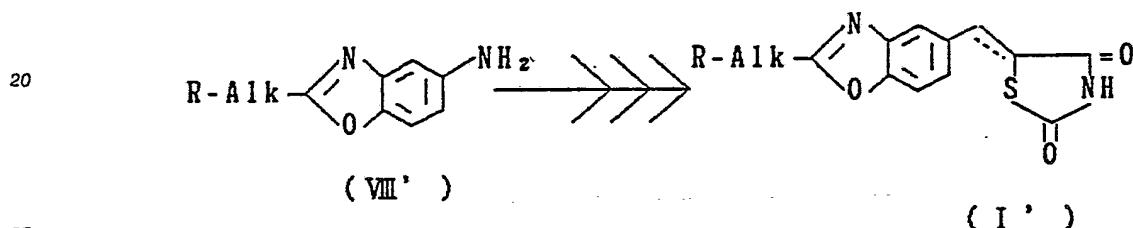
IR  $\nu$  <sub>max</sub> <sup>Nujol</sup> (cm<sup>-1</sup>):3180,1745,1680

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Examples 2 to 4

15 The corresponding starting compounds are treated in the same manner as described in Example 1 to give the compounds shown in Table 2.

Table 2



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(wherein the group  $\text{--}\text{CH}_2\text{--}$  is methylene group)

Ex. No.	Compound(I')	Properties
	R-Alk-	
2		M.p. 107 to 110 °C Mass(m/e):344(M <sup>+</sup> ) IR*:1770, 1685
3		M.p. 209 to 212 °C Mass(m/e):358,360(M <sup>+</sup> ) IR*:1760, 1740, 1700, 1685
4		M.p. 219 to 222 °C Mass(m/e):350(M <sup>+</sup> ) IR*:1740, 1680

\* : IR  $\nu_{\text{max}}^{\text{Nujol}} (\text{cm}^{-1})$  (same in the following Examples)

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### Example 5

(1) A solution containing 2.38 g of 2-phenyl-4-thiazoleacetyl chloride in 10 ml of tetrahydrofuran is added dropwise at 0 °C to the mixture of 3.10 g of 5-(3-amino-4-hydroxybenzyl)-2,4-dioxothiazolidine, 3.63 g of N,N-dimethylaniline, 25 ml of tetrahydrofuran and 5 ml of dimethylformamide, and the mixture is stirred at room temperature for 20 minutes. After the reaction, the mixture is poured into water, and extracted with ethyl acetate. The extract is washed, dried and evaporated to remove the solvent. The residue is crystallized with ethyl acetate, whereby 3.35 g of N-[5-(2,4-dioxothiazolidin-5-yl)methyl]-2-hydroxyphenyl]-2-phenylthiazole-4-acetamide are obtained.

40 Yield 76%  
M.p. 227 to 229 °C (decomp.)  
Mass(m/e):439(M<sup>+</sup>), 202  
IR  $\nu_{\text{max}}^{\text{Nujol}} (\text{cm}^{-1})$ :1740, 1690, 1670

(2) 1.5 g of the product obtained above are added to a trimethylsilyl polyphosphate solution prepared from 3.2 g of phosphorus pentaoxide, 6.6 ml of hexamethyldisiloxane, and 12.5 ml of 1,2-dichloroethane. The mixture is heated at 100 °C for 30 minutes. The reaction mixture is poured into ice-water, and extracted with ethyl acetate. The extract is dried, and evaporated to remove the solvent. The residue is recrystallized from methanol, whereby 880 mg of 5-[(2,4-dioxothiazolidin-5-yl)methyl]-2-[(2-phenyl-1,3-thiazol-4-yl)methyl]benzoxazole are obtained.

45 Yield 61%  
M.p. 86 to 89 °C  
Mass(m/e):421(M<sup>+</sup>), 305  
IR  $\nu_{\text{max}}^{\text{Nujol}} (\text{cm}^{-1})$ :1750, 1690

Example 6

5 (1) A mixture of 2.03 g of 2-phenyl-4-oxazoleacetic acid, 2.38 g of 5-(3-amino-4-hydroxybenzyl)-2,4-dioxothiazolidine, 2.06 g of dicyclohexylcarbodiimide, 2 ml of dimethylformamide and 20 ml of tetrahydrofuran is stirred at room temperature for 18 hours. After the reaction, insoluble materials are filtered off. The filtrate is poured into ice-water, and the solution is extracted with ethyl acetate. The extract is washed with water, dried and evaporated to remove the solvent. The residue is purified by silica gel column chromatography (solvent; chloroform : methanol = 10 : 1), whereby 2.83 g of N-[5-(2,4-dioxothiazolidin-5-yl)methyl-2-hydroxyphenyl]-2-phenyloxazole-4-acetamide are obtained.

10 Yield 67%

M.p. 197.5 to 199.5 °C

Mass(m/e):423(M<sup>+</sup>), 186

IR  $\nu$  <sub>max</sub> <sup>Nujol</sup> (cm<sup>-1</sup>):1740, 1690, 1670

15 (2) 635 mg of the product obtained above are heated at 230 °C for 40 minutes. After cooling, the reaction product is purified by silica gel column chromatography (solvent; chloroform : methanol = 10 : 1), and recrystallized from acetonitrile, whereby 383 mg of 5-[(2,4-dioxothiazolidin-5-yl)methyl]-2-[(2-phenyl-1,3-oxazol-4-yl)methyl]benzoxazole are obtained.

Yield 63%

M.p. 174 to 177.5 °C

20 Mass(m/e):405(M<sup>+</sup>), 289

IR  $\nu$  <sub>max</sub> <sup>Nujol</sup> (cm<sup>-1</sup>):1730, 1710

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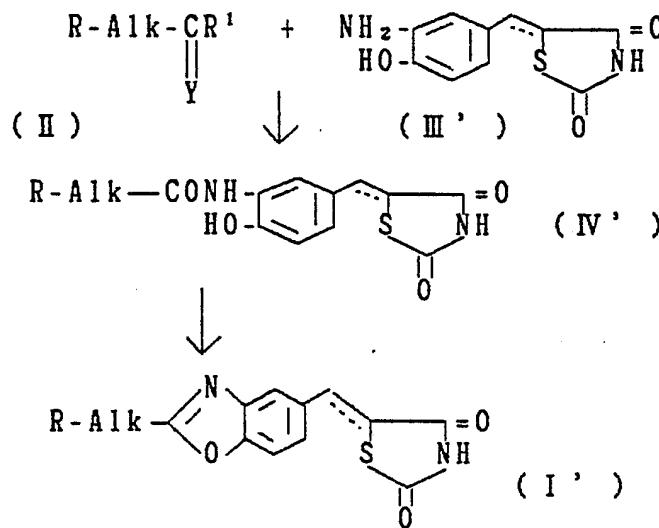
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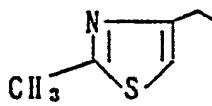
Examples 7 to 30

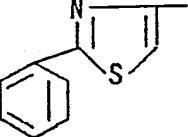
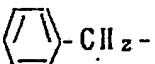
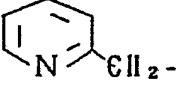
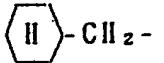
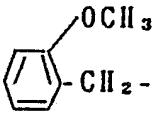
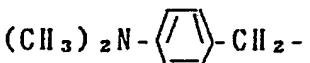
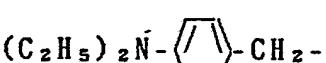
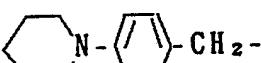
The corresponding starting compounds are treated in the same manner as described in Example 5-(1) and (2) or 6-(1) and (2) to give the compounds shown in Table 3.

Table 3

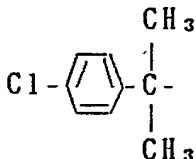
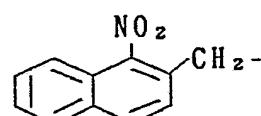
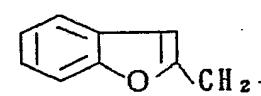
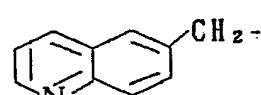
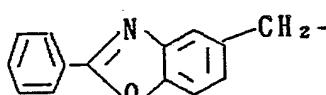


(wherein Y is oxygen atom, R<sup>1</sup> is hydrogen atom, and the group  $\text{C}_2\text{H}_4$  is methylene group)

Ex. No.	Compound(I')	Properties
	R-Alk-	
7		M.p. 167.5 to 168 °C Mass(m/e): 359 (M <sup>+</sup> ) IR*: 1740, 1700

8		M.p. 239 to 242 °C Mass(m/e): 407(M <sup>+</sup> ), 291 IR*: 1740, 1690
9		M.p. 158 to 159 °C Mass(m/e): 338(M <sup>+</sup> ), 222 IR*: 1750, 1690
10		M.p. 177 to 180 °C Mass(m/e): 339(M <sup>+</sup> ), 223 IR*: 1730, 1700
11		M.p. 86 to 89 °C Mass(m/e): 344(M <sup>+</sup> ), 262, 228 IR*: 1750, 1690
12		M.p. 79.5 to 81.0 °C Mass(m/e): 368(M <sup>+</sup> ) IR*: 1760, 1745, 1700
13		M.p. 217 to 218 °C Mass(m/e): 381(M <sup>+</sup> ) IR*: 1745, 1680
14		M.p. 162 to 163 °C Mass(m/e): 409(M <sup>+</sup> ) IR*: 1760, 1700
15		M.p. 229 to 232 °C Mass(m/e): 407(M <sup>+</sup> ) IR*: 1750, 1690
16		M.p. 205 to 208 °C Mass(m/e): 421(M <sup>+</sup> ) IR*: 1750, 1690

17		M.p. 213 to 215 °C Mass(m/e): 423(M <sup>+</sup> ) IR*: 1760, 1740, 1700
18		M.p. 161 to 171 °C Mass(m/e): 381(M <sup>+</sup> ) IR*: 1745, 1705
19		pale yellow powder Mass(m/e): 421(M <sup>+</sup> ) IR*: 1750, 1700
20		M.p. 183 to 186 °C Mass(m/e): 418(M <sup>+</sup> ) IR*: 1750, 1700
21		M.p. 201 to 202 °C Mass(m/e): 402(M <sup>+</sup> ) IR*: 1735, 1700
22		M.p. 153 to 155 °C Mass(m/e): 396(M <sup>+</sup> ) IR*: 1740, 1725, 1705
23		M.p. 165 to 167 °C Mass(m/e): 367(M <sup>+</sup> ) IR*: 1770, 1740, 1700
24		M.p. 180 to 183 °C Mass(m/e): 348(M <sup>+</sup> ) IR*: 2220, 1750, 1690
25		M.p. 129 to 132 °C Mass(m/e): 402, 400(M <sup>+</sup> ) IR*: 1755, 1730, 1690

26		M.p. 154 to 156 °C Mass(m/e): 402, 400(M <sup>+</sup> ) IR*: 1755, 1730, 1690, 1670
27		M.p. 183 to 184 °C Mass(m/e): 433(M <sup>+</sup> ) IR*: 1745, 1705
28		M.p. 158 to 160 °C Mass(m/e): 378(M <sup>+</sup> ) IR*: 1750, 1730, 1690
29		M.p. 251.5 to 254 °C Mass(m/e): 389(M <sup>+</sup> ) IR*: 1740, 1695
30		M.p. 208 to 210 °C Mass(m/e): 455(M <sup>+</sup> ) IR*: 1740, 1700

Example 31

40 A mixture of 4.0 g of phosphorus pentoxide, 10 ml of hexamethyldisiloxane, and 20 ml of 1,2-dichlorobenzene is refluxed for 5 minutes to give a trimethylsilyl polyphosphate solution. Then, 1.52 g of 2-phenyl-5-methyl-4-oxazoleacetic acid and 2.17 g of 5-(3-amino-4-hydroxybenzyl)-2,4-dioxothiazolidine are added thereto, and the mixture is heated at 150 °C for 2 hours. The reaction mixture is poured into ice-water, and extracted with ethyl acetate. The extract is washed with water, dried and evaporated to remove the solvent. The residue is purified by silica gel column chromatography (solvent; chloroform : methanol = 100 : 1), and recrystallized from a mixture of ethyl acetate and n-hexane, whereby 1.99 g of 5-[(2,4-dioxothiazolidin-5-yl)methyl]-2-[(2-phenyl-5-methyl-1,3-oxazol-4-yl)methyl]benzoxazole are obtained. Yield 68%  
M.p. 175 to 178 °C

50 Mass(m/e): 419(M<sup>+</sup>), 348, 303  
IR  $\nu$  <sub>max</sub> (cm<sup>-1</sup>): 1745, 1700, 1640

Examples 32 to 72

The corresponding starting compounds are treated in the same manner as described in Example 31 to give the compounds shown in Table 4.

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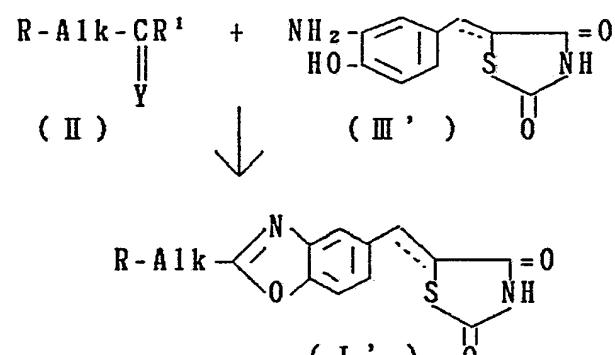
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Table 4



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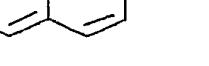
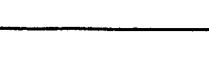
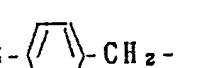
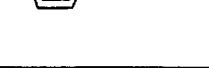
(part 1)(wherein Y is oxygen atom, R<sup>1</sup> is hydrogen atom, and the group — is methylene group)

Ex. No.	Compound(I')	Properties
	R-Alk-	
32		M.p. 86 to 89 °C Mass(m/e):427(M <sup>+</sup> ), 372, 359 IR*:1770, 1690
33		M.p. 146 to 148 °C Mass(m/e):425(M <sup>+</sup> ) IR*:1760, 1680
34		M.p. 288 to 289 °C Mass(m/e):480(M <sup>+</sup> ), 458 IR*:1665, 1565
35		M.p. 174.5 to 176 °C Mass(m/e):391(M <sup>+</sup> ) IR*:1740, 1700
36		M.p. 177 to 179 °C Mass(m/e):357(M <sup>+</sup> ) IR*:1770, 1740, 1700
37		M.p. 183 to 186 °C Mass(m/e):356(M <sup>+</sup> ) IR*:1740, 1690
38		M.p. 143 to 146 °C Mass(m/e):368(M <sup>+</sup> ) IR*:1760, 1740, 1710

39	<chem>CH3-c1ccccc1-CH2-</chem>	M.p. 180 to 183 °C Mass(m/e): 352(M <sup>+</sup> ) IR*: 1760, 1740, 1710
40	<chem>CF3-c1ccccc1-CH2-</chem>	M.p. 173 to 174 °C Mass(m/e): 406(M <sup>+</sup> ) IR*: 1750, 1730, 1690
41	<chem>Cl-c1ccccc1-CH2-Cl</chem>	M.p. 156.5 to 159.5 °C Mass(m/e): 406, 408, 410(M <sup>+</sup> ) IR*: 1740, 1700
42	<chem>CS1(=O)C=C1-CH2-</chem>	M.p. 139 to 141 °C Mass(m/e): 344(M <sup>+</sup> ) IR*: 1750, 1690
43	<chem>NO2-c1ccccc1-CH2-</chem>	M.p. 118 to 121 °C Mass(m/e): 383(M <sup>+</sup> ) IR*: 1720, 1700
44	<chem>Cl-c1ccccc1-CH2CH2-</chem>	M.p. 75 to 78 °C Mass(m/e): 386, 388(M <sup>+</sup> ) IR*: 1750, 1690
45	<chem>Cl-c1ccccc1-CH2-</chem>	M.p. 139 to 141 °C Mass(m/e): 372, 374(M <sup>+</sup> ) IR*: 1740, 1700
46	<chem>Cl-c1ccccc1-CH2-</chem>	M.p. 170.5 to 172 °C Mass(m/e): 372, 374(M <sup>+</sup> ) IR*: 1745, 1700
47	<chem>c1ccccc1-c2ccccc2-CH2-</chem>	M.p. 194 to 197 °C Mass(m/e): 414(M <sup>+</sup> ) IR*: 1745, 1680

48		M.p. 150 to 152.5 °C Mass(m/e):388(M <sup>+</sup> ) IR*:1745, 1690
49		M.p. 208.5 to 210.5 °C Mass(m/e):388(M <sup>+</sup> ) IR*:1745, 1680
50		colorless powder Mass(m/e):388, 386(M <sup>+</sup> ) IR*:1750, 1690
51		colorless powder Mass(m/e):420(M <sup>+</sup> ) IR*:1750, 1695
52		colorless powder Mass(m/e):414(M <sup>+</sup> ) IR*:1750, 1690
53		M.p. 175 to 178 °C Mass(m/e):428(M <sup>+</sup> ) IR*:1740, 1690
54		colorless powder Mass(m/e):416, 414(M <sup>+</sup> ) IR*:1750, 1695
55		M.p. 137 to 140 °C Mass(m/e):368(M <sup>+</sup> ) IR*:1745, 1705
56		M.p. 165 to 168 °C Mass(m/e):382(M <sup>+</sup> ) IR*:1745, 1705

57	<chem>C4H9Oc1ccccc1Cc2ccccc2</chem>	M.p. 155 to 157 °C Mass(m/e):410(M <sup>+</sup> ) IR*:1750, 1690
58	<chem>c1ccccc1Oc2ccccc2Cc3ccccc3</chem>	M.p. 122 to 123 °C Mass(m/e):430(M <sup>+</sup> ) IR*:1745, 1690
59	<chem>c1ccccc1Cc2ccccc2Oc3ccccc3</chem>	M.p. 138 to 141 °C Mass(m/e):444(M <sup>+</sup> ) IR*:1745, 1685
60	<chem>CC(=O)c1ccccc1Cc2ccccc2Oc3ccccc3</chem>	M.p. 163 to 166 °C Mass(m/e):398(M <sup>+</sup> ) IR*:1745, 1700
61	<chem>CC(=O)c1ccccc1Cc2ccccc2Oc3ccccc3</chem>	M.p. 190 to 193 °C Mass(m/e):428(M <sup>+</sup> ) IR*:1750, 1700
62	<chem>CN1Cc2ccccc2Cc3ccccc3</chem>	M.p. 183 to 185 °C Mass(m/e):403(M <sup>+</sup> ) IR*:1750, 1700
63	<chem>CC(=O)c1ccccc1Cc2ccccc2N(C2H5)2</chem>	foam Mass(m/e):409(M <sup>+</sup> ) IR*:1750, 1700
64	<chem>CC(=O)c1ccccc1Cc2ccccc2Cc3ccccc3</chem>	M.p. 203 to 205.5 °C Mass(m/e):418(M <sup>+</sup> ) IR*:1750, 1690
65	<chem>CC(=O)c1ccccc1Cc2ccccc2Cc3ccccc3</chem>	M.p. 225.5 to 227.5 °C Mass(m/e):402(M <sup>+</sup> ) IR*:1745, 1685

66		M.p. 214 to 216 °C Mass (m/e) : 424, 422 (M <sup>+</sup> ) IR * : 1750, 1680
67		M.p. 144 to 147 °C Mass (m/e) : 384 (M <sup>+</sup> ) IR * : 1740, 1700
68		M.p. 159 to 162 °C Mass (m/e) : 394 (M <sup>+</sup> ) IR * : 1760, 1740, 1700
69		M.p. 188 to 189 °C Mass (m/e) : 352 (M <sup>+</sup> ) IR * : 1740, 1710, 1680

(part 2) (wherein Y is oxygen atom, R<sup>1</sup> is hydrogen atom, and the group  $\wedge$  is methine group)

Ex. No.	Compound(I')	Properties
	R-Alk-	
70		M.p. 261.5 to 263 °C Mass(m/e):417(M <sup>+</sup> ) IR*:1740, 1720, 1700
71		M.p. 221 to 222.5 °C Mass(m/e):419(M <sup>+</sup> ) IR*:1740, 1705
72		M.p. 218 to 219.5 °C Mass(m/e):372, 370(M <sup>+</sup> ) IR*:1735, 1705

note): \*): sodium salt

Example 73

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A mixture of 500 mg of 5-(3-amino-4-hydroxybenzyl)-2,4-dioxothiazolidine, 405 mg of 2-phenyl-4-formylthiazole and 30 ml of ethanol is refluxed for 20 minutes, and the solvent is distilled off. 840 mg of 4-(2,4-dioxothiazolidin-5-yl)methyl-2-[(phenylthiazol-4-yl)methylidene]aminophenol obtained as a crude product are dissolved in 40 ml of benzene, and 1.26 g of lead tetraacetate are added thereto. After the mixture 10 is stirred at room temperature for 15 minutes, the solvent is distilled off. Ethyl acetate and water are added to the residue, and the ethyl acetate layer is washed with water, dried, and evaporated to remove the solvent. The residue is purified by silica gel column chromatography (solvent; chloroform : methanol = 100 : 1), whereby 400 mg of 5-[(2,4-dioxothiazolidin-5-yl)methyl]-2-(2-phenyl-1,3-thiazol-4-yl)benzoxazole are obtained. The Mass and IR data of this product are identical with those of the product obtained in Example 15 8.

Example 74

20 (1) 9.47 g of N-(5-amino-2-hydroxyphenyl)-2-(4-chlorophenyl)acetamide are treated in the same manner as described in Example 1-(1) to (3) to give 5.64 g of N-[5-(2,4-dioxothiazolidin-5-yl)methyl-2-hydroxyphenyl]-2-(4-chlorophenyl)acetamide as pale yellow powder.

M.p. 207 to 209 °C

Mass(m/e):392, 390(M<sup>+</sup>)25 IR <sub>max</sub><sup>Nujol</sup> (cm<sup>-1</sup>):1750, 1720

(2) 5.64 g of the product obtained above are heated at 220 °C for 50 minutes. After cooling, the products are purified by silica gel column chromatography (solvent; chloroform : methanol = 50 : 1), and recrystallized from ether, whereby 4.0 g of 5-[(2,4-dioxothiazolidin-5-yl)methyl]-2-(4-chlorobenzyl)-benzoxazole are obtained.

30 M.p. 169.5 to 170.5 °C

Mass(m/e):374, 372(M<sup>+</sup>)IR <sub>max</sub><sup>Nujol</sup> (cm<sup>-1</sup>):1750, 1690Example 75

N-(5-amino-2-hydroxyphenyl)-4-hydroxy-3,5-di(tert.-butyl)benzamide is treated in the same manner as described in Example 74 to give 5-[(2,4-dioxothiazolidin-5-yl)methyl]-2-[4-hydroxy-3,5-di(tert.-butyl)phenyl]-benzoxazole.

40 M.p. 213 to 216 °C

Mass(m/e):452(M<sup>+</sup>)IR <sub>max</sub><sup>Nujol</sup> (cm<sup>-1</sup>):1750, 1700Example 76

N-(4-amino-2-hydroxyphenyl)-2-(4-chlorophenyl)acetamide is treated in the same manner as described in Example 74 to give 6-[(2,4-dioxothiazolidin-5-yl)methyl]-2-[4-chlorobenzyl]benzoxazole.

M.p. 219.5 to 220.5 °C

50 Mass(m/e):374, 372(M<sup>+</sup>)IR <sub>max</sub><sup>Nujol</sup> (cm<sup>-1</sup>):1745, 1695Example 77

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3.48 g of 5-[(2,4-dioxothiazolidin-5-yl)methyl]-2-(4-nitrobenzyl)benzoxazole are dissolved in a mixture of 70 ml of tetrahydrofuran and 70 ml of methanol, and 2.5 g of 10% palladium-carbon are added thereto. The mixture is subjected to catalytic hydrogenation in hydrogen gas atmosphere under atmospheric pressure.

Insoluble materials are filtered off, and the filtrate is condensed. The residue is purified by silica gel column chromatography (solvent: chloroform : methanol = 20 : 1) and recrystallized from ethyl acetate, whereby 1.86 g of 5-[(2,4-dioxothiazolidin-5-yl)methyl]-2-(4-aminobenzyl)benzoxazole are obtained.

M.p. 180 to 183 °C

5 Mass(m/e):353(M<sup>+</sup>)

IR  $\nu$ <sub>max</sub> (cm<sup>-1</sup>):1735, 1700

Example 78

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A mixture of 0.99 g of 5-[(2,4-dioxothiazolidin-5-yl)methyl]-2-(4-aminobenzyl)benzoxazole, 2 ml of acetic anhydride and 10 ml of pyridine is stirred at room temperature overnight. 10% Hydrochloric acid is added thereto, and the solution is extracted with ethyl acetate. The extract is washed with water, dried and evaporated to remove the solvent. The residue is recrystallized from ethyl acetate, whereby 0.56 g of 5-[(2,4-dioxothiazolidin-5-yl)methyl]-2-(4-acetamidobenzyl)benzoxazole is obtained.

15 M.p. 233 to 236 °C

Mass(m/e):395(M<sup>+</sup>)

IR  $\nu$ <sub>max</sub> (cm<sup>-1</sup>):1745, 1690

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Example 79

A mixture of 1.0 g of 5-[(2,4-dioxothiazolidin-5-yl)methyl]-2-(4-methylthiobenzyl)benzoxazole, 0.58 g of 80% m-chloroperbenzoic acid and 25 ml of methylene chloride is stirred at room temperature for 10 minutes. The solvent is distilled off, and ethyl acetate is added to the residue. The ethyl acetate solution is washed, dried and evaporated to remove the solvent. The residue is purified by silica gel column chromatography (solvent: chloroform : methanol = 20 : 1), whereby 0.67 g of 5-[(2,4-dioxothiazolidin-5-yl)methyl]-2-(4-methylsulfinylbenzyl)benzoxazole are obtained as colorless foam.

Yield 64 %

30 Mass(m/e):400(M<sup>+</sup>)

IR  $\nu$ <sub>max</sub> (cm<sup>-1</sup>):1750, 1690

Example 80

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A mixture of 1.2 g of 5-[(2,4-dioxothiazolidin-5-yl)methyl]-2-(4-methylthiobenzyl)benzoxazole, 2.1 g of 80% m-chloroperbenzoic acid and 30 ml of methylene chloride is stirred at room temperature for 20 minutes. The reaction mixture is treated in the same manner as described in Example 79, and recrystallized from a mixture of tetrahydrofuran and n-hexane, whereby 1.2 g of 5-[(2,4-dioxothiazolidin-5-yl)methyl]-2-(4-methylsulfonylbenzyl)benzoxazole are obtained as colorless powder.

40 Yield 69 %

M.p. 168 to 169 °C

45 Example 81

1.3 g of 5-[(2,4-dioxothiazolidin-5-yl)methyl]-2-(benzoyl)benzoxazole are dissolved in a mixture of 30 ml of methanol and 6 ml of tetrahydrofuran, and 0.14 g of sodium borohydride is added thereto. After the mixture is stirred at room temperature for 5 minutes, water is added thereto. The solution is extracted with ethyl acetate, and the extract is evaporated to remove the solvent. The residue is crystallized with ether, whereby 0.64 g of 5-[(2,4-dioxothiazolidin-5-yl)methyl]-2-( $\alpha$ -hydroxybenzyl)benzoxazole is obtained as colorless crystal.

50 M.p. 210 to 212 °C (decomp.)

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Example 82

A mixture of 0.95 g of 5-[(2,4-dioxothiazolidin-5-yl)methyl]-2-(4-benzyloxybenzyl)benzoxazole, 10 ml of a 25 % hydrogen bromide solution in acetic acid and 10 ml of acetic acid is stirred at room temperature 5 overnight. Ethyl acetate and water are added to the reaction mixture. The ethyl acetate layer is washed with water, dried and evaporated to remove the solvent. The residue is crystallized with n-hexane, and recrystallized from a mixture of ethyl acetate and n-hexane, whereby 0.42 g of 5-[(2,4-dioxothiazolidin-5-yl)-methyl]-2-(4-hydroxybenzyl)benzoxazole is obtained as colorless needles.

Yield 55 %  
 10 M.p. 201 to 204 °C  
 Mass(m/e):354(M<sup>+</sup>)  
 IR  $\nu$  Nujol max (cm<sup>-1</sup>):3340, 1730, 1690

Example 83

(1) 5-(3-amino-4-hydroxybenzyl)-2,4-dioxothiazolidine and 4-(N,N-dimethylamino)phenylacetyl chloride, prepared from 4-(N,N-dimethylamino)phenylacetic acid and oxalyl chloride, are treated in the same manner as described in Example 5-(1) to give N-[5-(2,4-dioxothiazolidin-5-yl)methyl-2-hydroxyphenyl]-2-(4-dimethylaminophenyl)acetamide.

20 M.p. 215.5 to 217.5 °C  
 (2) A mixture of 6.0 g of the product obtained above, 0.3 g of p-toluenesulfonic acid monohydrate and 35 ml of diethylaniline is refluxed for 1.5 hours. After cooling, the precipitated crystals are collected by filtration. The crystals are washed and recrystallized from a mixture of tetrahydrofuran and methanol, 25 whereby 4.9 g of 5-[(2,4-dioxothiazolidin-5-yl)methyl]-2-(4-dimethylaminobenzyl)benzoxazole are obtained. Yield 78 %  
 M.p. 217 to 218 °C

## 30 (Preparation of Starting Compounds)

Preparation 1

(1) A solution of 6.16 g of 2-amino-4-nitrophenol and 4.77 g of benzaldehyde in ethanol is refluxed. The 35 reaction solution is condensed and cooled. The crystalline precipitates are collected by filtration to give 2-benzylideneamino-4-nitrophenol. 15.5 g of lead tetraacetate are added to a benzene suspension of the product obtained above, and the mixture is stirred. After the reaction, insoluble materials are filtered off. The filtrate is washed, and condensed. The residue is purified by silica gel column chromatography and recrystallized from ethanol, whereby 5.08 g of 5-nitro-2-phenylbenzoxazole are obtained.

40 M.p. 169 to 171.5 °C  
 (2) 3 g of 10% palladium-carbon are added to an acetic acid solution of 8.85 g of the product obtained above, and the mixture is subjected to catalytic hydrogenation in hydrogen gas atmosphere. Insoluble materials are filtered off, and the filtrate is condensed. The residue is recrystallized from a mixture of chloroform and n-hexane, whereby 7.02 g of 5-amino-2-phenylbenzoxazole are obtained. M.p. 150.5 to 153 45 °C

Preparation 2

50 (1) 16.0 g of (1-methylcyclohexyl)carbonyl chloride are added dropwise to a tetrahydrofuran solution of 14.7 g of 2-amino-4-nitrophenol and 12.1 g of N,N-dimethylaniline under ice-cooling, and the mixture is stirred at room temperature. 10% Hydrochloric acid is added to the reaction mixture, and the crystals are collected by filtration. The crystals are added to 260 ml of thionyl chloride, then the mixture is refluxed. Thionyl chloride which remains unreacted is distilled off, and the residue is purified by silica gel column 55 chromatography, whereby 21.7 g of 2-(1-methylcyclohexyl)-5-nitrobenzoxazole are obtained.

M.p. 57 to 59 °C

(2) The product obtained above is treated in the same manner as described in Preparation 1-(2) to give 5-amino-2-(1-methylcyclohexyl)benzoxazole as a colorless oil.  
Mass(m/e):230(M<sup>+</sup>)

5

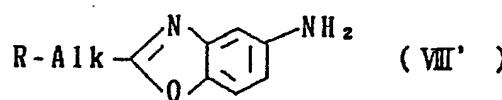
Preparations 3 and 4

The corresponding starting compounds are treated in the same manner as described in Preparation 1  
10 or 2 to give the compounds shown in Table 5.

15

Table 5

20



25

Pr. No.	Compound(VIII') R-Alk-	Properties	
3	C1 -	M.p. 177 to 180 °C	
4	-CH=CH-	M.p. 148 to 150.5 °C	

50

Preparation 5

55

(1) A mixture of 8.55 g of 4-chlorophenylacetic acid and 35 ml of thionyl chloride is heated. After the reaction, thionyl chloride is distilled off. The residue is added to a tetrahydrofuran solution of 7.70 g of 2-amino-4-nitrophenol and 6.65 g of N,N-dimethylaniline, and the mixture is stirred at room temperature. The solvent is distilled off, and diluted hydrochloric acid is added to the residue. Then, the crystals are collected by filtration, whereby 14.2 g of N-(5-nitro-2-hydroxyphenyl)-2-(4-chlorophenyl)acetamide are obtained.

M.p. 250 to 252 °C (decomp.)

(2) 13.93 g of the product obtained above are added to a ethanol-ethyl acetate suspension of tin(II)

chloride, and the mixture is heated. After the reaction, the solvent is distilled off, and the residue is neutralized with sodium hydroxide. The mixture is extracted with ethyl acetate. The extract is evaporated to remove the solvent, and the residue is recrystallized from ethyl acetate, whereby 9.86 g of N-(5-amino-2-hydroxyphenyl)-2-(4-chlorophenyl)acetamide are obtained.

5 M.p. 164 to 167 °C

#### Preparation 6

10 4-hydroxy-3,5-di(tert.-butyl)benzoic acid and 2-amino-4-nitrophenol are treated in the same manner as described in Preparation 5-(1) and Preparation 1-(2) to give N-(5-amino-2-hydroxyphenyl)-4-hydroxy-3,5-di-(tert.-butyl)benzamide are obtained.

M.p. 222 to 225 °C (decomp.)

15

#### Preparation 7

(1) 4-aminophenol is treated in the same manner as described in Example 1-(1) to (3) to give 5-(4-hydroxybenzyl)-2,4-dioxothiazolidine.

20 M.p. 157 to 158.5 °C

(2) 5.19 g of the product obtained above are added to 50 ml of 70% nitric acid under ice-cooling, and the mixture is stirred for 5 minutes. The reaction mixture is poured into ice-water, and extracted with ethyl acetate. The extract is washed with water, dried, and evaporated to remove the solvent. The residue is recrystallized from a mixture of ethyl acetate and n-hexane, whereby 4.85 g of 5-(4-hydroxy-3-nitrobenzyl)-2,4-dioxothiazolidine are obtained.

25 Yield 78 %

M.p. 141 to 143.5 °C

(3) 10% palladium-carbon, 4M-aqueous sodium hypophosphite solution and water are added to a dimethylformamide solution of 1.0 g of the product obtained above, and the mixture is stirred at room 30 temperature. After the reaction, insoluble materials are filtered off. Water is added to the filtrate, and the solution is extracted with ethyl acetate. The extract is evaporated to remove the solvent, and the residue is recrystallized from isopropylalcohol, whereby 755 mg of 5-(3-amino-4-hydroxybenzyl)-2,4-dioxothiazolidine are obtained.

M.p. 215 to 217.5 °C (decomp.)

35

#### Preparation 8

(1) A mixture of 18.0 g of 4-hydroxy-3-nitrobenzaldehyde, 12.74 g of 2,4-dioxothiazolidine, 2.2 ml of 40 piperidine and 180 ml of dioxane is refluxed for 13 hours. After cooling, 100 ml of water and 10 ml of 10% hydrochloric acid are added thereto. The crystalline precipitates are collected by filtration, dried, and recrystallized from a mixture of tetrahydrofuran and n-hexane, whereby 14.8 g of 5-(4-hydroxy-3-nitrobenzylidene)-2,4-dioxothiazolidine are obtained.

Yield 52 %

45 M.p. 256.5 to 258 °C

(2) 12.85 g of the product obtained above are treated in the same manner as described in Preparation 7-(3) and the filtrate is poured into water. The crystalline precipitates are collected by filtration, whereby 10.86 g of 5-(3-amino-4-hydroxybenzylidene)-2,4-dioxothiazolidine are obtained.

Yield 95 %

50 M.p. 260.5 to 261.5 °C

#### Preparation 9

55 (1) A solution of 13.3 g of L-4-hydroxy-3-nitrophenylalanine and 35 g of potassium bromide in 170 ml of an aqueous 3N-sulfuric acid is cooled in ice-bath. Then, a solution of 4.95 g of sodium nitrite in 10 ml of water is added dropwise to the mixture for 30 minutes. After the reaction at the same temperature for 10 minutes, the mixture is extracted with ethyl acetate. The ethyl acetate layer is washed with water, dried and

evaporated to remove the solvent, whereby 15.2 g of 2-bromo-3-(4-hydroxy-3-nitrophenyl)propionic acid are obtained as brown solid.

(2) A mixture of 15.1 g of the product obtained above, 6.14 g of thiourea, 5.51 g of sodium acetate and 150 ml of ethanol is refluxed for 3 hours. The solvent is distilled off, and water is added to the residue. The precipitates are collected by filtration, washed, and dried, whereby 12.2 g of 5-(4-hydroxy-3-nitrobenzyl)-2-imino-4-oxothiazolidine are obtained as yellow powder.

M.p. 221 to 223 °C (decomp.)

(3) A mixture of 12.1 g of the product obtained above, 15.6 ml of conc. hydrochloric acid, 125 ml of ethylene glycol monomethyl ether and 12.5 ml of water is refluxed for 4 hours. The reaction mixture is condensed and the residue is extracted with ethyl acetate. The ethyl acetate layer is washed with water, dried, and evaporated to remove the solvent. The residue is recrystallized from a mixture of ethyl acetate and n-hexane, whereby 10.4 g of 5-(4-hydroxy-3-nitrobenzyl)-2,4-dioxothiazolidine are obtained as yellow powder.

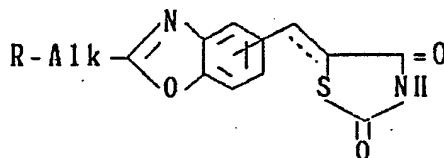
M.p. 141 to 143.5 °C

(4) 10.3 g of the product obtained above are dissolved in 170 ml of a mixture of tetrahydrofuran and methanol, and 2.5 g of 10% palladium-carbon are added thereto. The mixture is subjected to catalytic hydrogenation at atmospheric pressure. The catalyst is filtered off, and filtrate is condensed. Isopropyl alcohol is added to the residue, whereby 8.77 g of 5-(3-amino-4-hydroxybenzyl)-2,4-dioxothiazolidine are obtained as pale yellow powder.

M.p. 215 to 217.5 °C

### Claims

25 1. A benzoxazole derivative of the formula:



wherein R is a substituted or unsubstituted phenyl group, a substituted or unsubstituted naphthyl group, a substituted or unsubstituted cycloalkyl group or a substituted or unsubstituted heterocyclic group; Alk is single bond, a substituted or unsubstituted lower alkylene group, a lower alkenylene group or a lower alkynylene group; and the group  $\text{R}-\text{Alk}$  is a group of the formula:  $-\text{CH}_2-$  or  $-\text{CH}=$ , or a pharmaceutically acceptable salt thereof.

2. The compound claimed in Claim 1, in which R is phenyl group, naphthyl group, cyclohexyl group, 1,3-thiazol-4-yl group, 1,3-oxazol-4-yl group, pyridyl group, benzoxazolyl group, thiienyl group, quinolyl group or benzofuranyl group [these groups may optionally have a substituent or substituents selected from a (lower alkoxy)carbonyl group, a lower alkoxy group, a lower alkyl group, a trihalogeno-lower alkyl group, a lower alkylthio group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, phenyl group, phenoxy group, a phenyl-lower alkoxy group, hydroxy group, a halogen atom, nitro group, amino group, a lower alkanoylamino group, a di(lower alkyl)amino group, a cycloalkyl group, pyrrolidino group, piperidino group, morphorino group and pyrrolyl group.]; and Alk is single bond, a straight or branched lower alkylene group, a lower alkenylene group or a lower alkynylene group [said lower alkylene group may optionally be substituted with hydroxy group, oxygen atom, phenyl group or a cycloalkyl group.], or a pharmaceutically acceptable salt thereof.

50 3. The compound claimed in Claim 2, in which R is (1) a phenyl group which may optionally have 1 to 3 substituent(s) selected from a lower alkoxy group, a lower alkyl group, a trihalogeno-lower alkyl group, a lower alkylthio group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, phenyl group, a halogen atom, nitro group, pyrrolidino group, piperidino group, morphorino group, pyrrolyl group and a di(lower alkyl)amino group; (2) a naphthyl group which may optionally be substituted with a lower alkoxy group, a lower alkyl group, a halogen atom or nitro group; (3) a pyridyl group which may optionally be substituted with a lower alkyl group; or (4) a 1,3-thiazol-4-yl or 1,3-oxazol-4-yl group which may optionally have 1 to 2 substituent(s) selected from a lower alkyl group, a lower alkylthio group, a cycloalkyl group and phenyl group, or a pharmaceutically acceptable salt thereof.

4. The compound claimed in Claim 3, in which R is

- ① a phenyl group which may optionally have 1 to 2 substituent(s) selected from a C<sub>1</sub> to C<sub>4</sub> alkoxy group, a C<sub>1</sub> to C<sub>4</sub> trihalogenoalkyl group, a halogen atom, nitro group and a di(C<sub>1</sub> to C<sub>4</sub> alkyl)amino group;
- ② naphthyl group or
- ③ a 1,3-thiazol-4-yl or 1,3-oxazol-4-yl group which may optionally have 1 to 2 substituent(s) selected from a C<sub>1</sub> to C<sub>4</sub> alkyl group and phenyl group, or a pharmaceutically acceptable salt thereof.

5. The compound claimed in Claim 2, 3 or 4 in which Alk is a straight or branched C<sub>1</sub> to C<sub>4</sub> alkylene group, or a pharmaceutically acceptable salt thereof.

6. The compound claimed in Claim 5 in which 2,4-dioxothiazolidin-5-yl(or ylidene)-methyl group is bound to benzoxazole ring at the 5-or 6-position thereof, or a pharmaceutically acceptable salt thereof.

10. The compound claimed in Claim 5 in which 2,4-dioxothiazolidin-5-yl(or ylidene)-methyl group is bound to benzoxazole ring at the 5-position thereof, or a pharmaceutically acceptable salt thereof.

15. The compound claimed in Claim 7 in which R is a phenyl group substituted with a C<sub>1</sub> to C<sub>4</sub> alkoxy group or a di(C<sub>1</sub> to C<sub>4</sub> alkyl)amino group, or naphthyl group, Alk is a straight C<sub>1</sub> to C<sub>4</sub> alkylene group, and a group  $\begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$  is methylene group, or a pharmaceutically acceptable salt thereof.

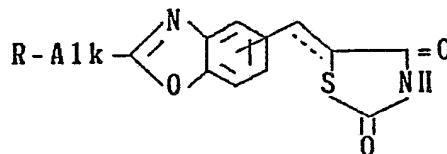
20. The compound claimed in Claim 8 in which R is methoxyphenyl group, dimethylaminophenyl group or naphthyl group, and Alk is methylene group, or a pharmaceutically acceptable salt thereof.

25. 10. 5-[(2,4-dioxothiazolidin-5-yl)methyl]-2-(4-methoxybenzyl)benzoxazole or a pharmaceutically acceptable salt thereof.

11. 5-[(2,4-dioxothiazolidin-5-yl)methyl]-2-(4-dimethylaminobenzyl)benzoxazole or a pharmaceutically acceptable salt thereof.

12. 5-[(2,4-dioxothiazolidin-5-yl)methyl]-2-[(2-naphthyl)methyl]benzoxazole or a pharmaceutically acceptable salt thereof.

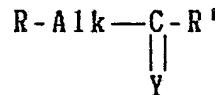
25. 13. A process for preparing a benzoxazole derivative of the formula:



wherein R is a substituted or unsubstituted phenyl group, a substituted or unsubstituted naphthyl group, a substituted or unsubstituted cycloalkyl group or a substituted or unsubstituted heterocyclic group; Alk is single bond, a substituted or unsubstituted lower alkylene group, a lower alkenylene group or a lower alkynylene group; the group  $\begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$  is a group of the formula: -CH<sub>2</sub>- or -CH=, or a pharmaceutically acceptable salt thereof, which comprises the step or steps of:

40 (1) condensing a compound of the formula:

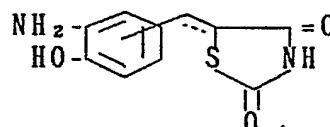
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wherein R<sup>1</sup> is hydroxy group, a lower alkoxy group or a reactive residue, Y is oxygen atom or imino group, and R and Alk are the same as defined above, or a salt thereof with a dioxothiazolidine compound of the formula:

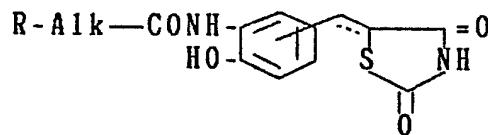
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wherein the symbol is the same as defined above, or a salt thereof,

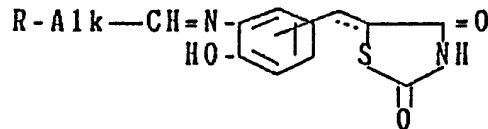
(2) dehydrating an amide of the formula:

5



10 wherein the symbols are the same as defined above, or a salt thereof or,  
 (3) dehydrogenating an azomethine compound of the formula:

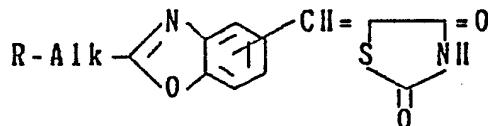
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20 wherein the symbols are the same as defined above, or a salt thereof, and  
 (4) if required, converting the product into a pharmaceutically acceptable salt thereof.

14. A process for preparing a benzoxazole derivative of the formula:

25



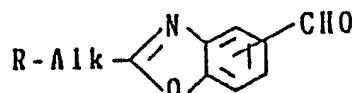
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wherein R is a substituted or unsubstituted phenyl group, a substituted or unsubstituted naphthyl group, a substituted or unsubstituted cycloalkyl group or a substituted or unsubstituted heterocyclic group; Alk is single bond, a substituted or unsubstituted lower alkylene group, a lower alkenylene group or a lower alkynylene group, or a salt thereof, which comprises the step of:

35

reacting the aldehyde compound of the formula:

40

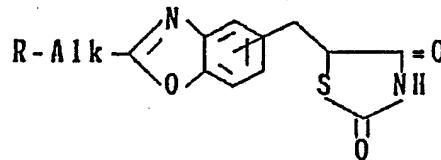


wherein the symbols are the same as defined above, or a salt thereof with 2,4-dioxothiazolidine or a salt thereof.

45

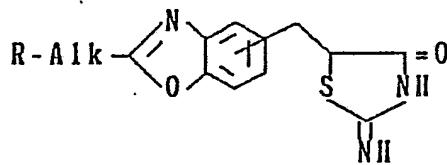
15. A process for preparing a benzoxazole derivative of the formula:

50



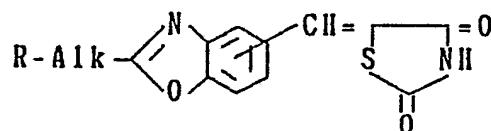
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wherein R is a substituted or unsubstituted phenyl group, a substituted or unsubstituted naphthyl group, a substituted or unsubstituted cycloalkyl group or a substituted or unsubstituted heterocyclic group; Alk is single bond, a substituted or unsubstituted lower alkylene group, a lower alkenylene group or a lower alkynylene group, or a salt thereof, which comprises the step of:  
 hydrolysis of an imino compound of the formula:



wherein the symbols are the same as defined above, or a salt thereof, or reduction of the compound of the formula:

10



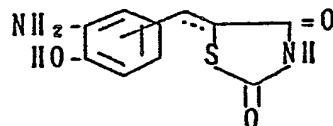
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wherein the symbols are the same as defined above, or a salt thereof.

16. A pharmaceutical composition which comprises a pharmaceutically effective amount of the compound claimed in Claim 1 and a pharmaceutically acceptable carrier thereof.

20 17. A compound of the formula:

25



30 wherein the group is a group of the formula: -CH<sub>2</sub>- or -CH=, or a salt thereof.

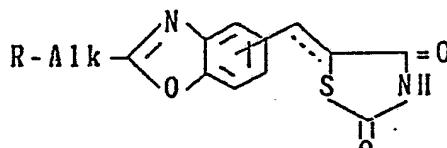
18. The use of a compound according to any of claims 1-12 for the manufacture of an anti-diabetic agent.

Claims for the following Contracting States : ES, GR

35

1. The use of a benzoxazole derivative of the formula:

40



45 wherein R is a substituted or unsubstituted phenyl group, a substituted or unsubstituted naphthyl group, a substituted or unsubstituted cycloalkyl group or a substituted or unsubstituted heterocyclic group; Alk is single bond, a substituted or unsubstituted lower alkylene group, a lower alkenylene group or a lower alkynylene group; and the group is a group of the formula: -CH<sub>2</sub>- or -CH=, or a pharmaceutically acceptable salt thereof for the manufacture of an anti-diabetic agent.

50 2. The use according to Claim 1, in which R is phenyl group, naphthyl group, cyclohexyl group, 1,3-thiazol-4-yl group, 1,3-oxazol-4-yl group, pyridyl group, benzoxazolyl group, thienyl group, quinolyl group or benzofuranyl group [these groups may optionally have a substituent or substituents selected from a (lower alkoxy)carbonyl group, a lower alkoxy group, a lower alkyl group, a trihalogeno-lower alkyl group, a lower alkylthio group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, phenyl group, phenoxy group, a phenyl-lower alkoxy group, hydroxy group, a halogen atom, nitro group, amino group, a lower alkanoylamino group, a di(lower alkyl)amino group, a cycloalkyl group, pyrrolidino group, piperidino group, morphorino group and pyrrolyl group.]; and Alk is single bond, a straight or branched lower alkylene group,

a lower alkenylene group or a lower alkynylene group [said lower alkylene group may optionally be substituted with hydroxy group, oxygen atom, phenyl group or a cycloalkyl group.], or a pharmaceutically acceptable salt thereof.

3. The use according to Claim 2, in which R is ① a phenyl group which may optionally have 1 to 3 substituent(s) selected from a lower alkoxy group, a lower alkyl group, a trihalogeno-lower alkyl group, a lower alkylthio group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, phenyl group, a halogen atom, nitro group, pyrrolidino group, piperidino group, morphorino group, pyrrolyl group and a di(lower alkyl)amino group; ② a naphthyl group which may optionally be substituted with a lower alkoxy group, a lower alkyl group, a halogen atom or nitro group; ③ a pyridyl group which may optionally be substituted with a lower alkyl group; or ④ a 1,3-thiazol-4-yl or 1,3-oxazol-4-yl group which may optionally have 1 to 2 substituent(s) selected from a lower alkyl group, a lower alkylthio group, a cycloalkyl group and phenyl group, or a pharmaceutically acceptable salt thereof.

4. The use according to Claim 3, in which R is

① a phenyl group which may optionally have 1 to 2 substituent(s) selected from a C<sub>1-4</sub> alkoxy group, a C<sub>1-4</sub> trihalogenoalkyl group, a halogen atom, nitro group and a di(C<sub>1-4</sub> alkyl)amino group;  
② naphthyl group or  
③ a 1,3-thiazol-4-yl or 1,3-oxazol-4-yl group which may optionally have 1 to 2 substituent(s) selected from a C<sub>1-4</sub> alkyl group and phenyl group, or a pharmaceutically acceptable salt thereof.

5. The use according to any of Claims 2-4 in which Alk is a straight or branched C<sub>1-4</sub> alkylene group, or a pharmaceutically acceptable salt thereof.

6. The use according to Claim 5 in which 2,4-dioxothiazolidin-5-yl(or ylidene)-methyl group is bound to benzoxazole ring at the 5-or 6-position thereof, or a pharmaceutically acceptable salt thereof.

7. The use according to Claim 5 in which 2,4-dioxothiazolidin-5-yl(or ylidene)-methyl group is bound to benzoxazole ring at the 5-position thereof, or a pharmaceutically acceptable salt thereof.

8. The use according to Claim 7 in which R is a phenyl group substituted with a C<sub>1-4</sub> alkoxy group or a di(C<sub>1-4</sub> alkyl)amino group, or naphthyl group, Alk is a straight C<sub>1-4</sub> alkylene group, and a group  $\text{--CH}_2\text{--}$  is methylene group, or a pharmaceutically acceptable salt thereof.

9. The use according to Claim 8 in which R is methoxyphenyl group, dimethylaminophenyl group or naphthyl group, and

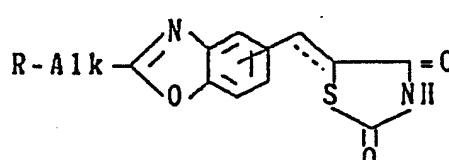
10. Alk is methylene group, or a pharmaceutically acceptable salt thereof.

10. The use according to Claim 1 wherein the derivative is 5-[(2,4-dioxothiazolidin-5-yl)methyl]-2-(4-methoxybenzyl)benzoxazole or a pharmaceutically acceptable salt thereof.

11. The use according to Claim 1 wherein the derivative is 5-[(2,4-dioxothiazolidin-5-yl)methyl]-2-(4-dimethylaminobenzyl)benzoxazole or a pharmaceutically acceptable salt thereof.

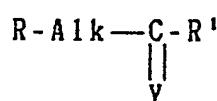
12. The use according to Claim 1 wherein the derivative is 5-[(2,4-dioxothiazolidin-5-yl)methyl]-2-[(2-naphthyl)methyl]benzoxazole or a pharmaceutically acceptable salt thereof.

13. A process for preparing a benzoxazole derivative of the formula:



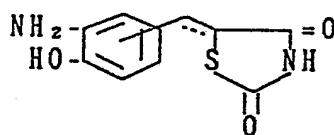
45 wherein R is a substituted or unsubstituted phenyl group, a substituted or unsubstituted naphthyl group, a substituted or unsubstituted cycloalkyl group or a substituted or unsubstituted heterocyclic group; Alk is single bond, a substituted or unsubstituted lower alkylene group, a lower alkenylene group or a lower alkynylene group; the group  $\text{--CH}_2\text{--}$  is a group of the formula:  $-\text{CH}_2-$  or  $-\text{CH}=\text{}$ , or a pharmaceutically acceptable salt thereof, which comprises the step or steps of:

(1) condensing a compound of the formula:



wherein R<sup>1</sup> is hydroxy group, a lower alkoxy group or a reactive residue, Y is oxygen atom or imino group, and R and Alk are the same as defined above, or a salt thereof with a dioxothiazolidine compound of the formula:

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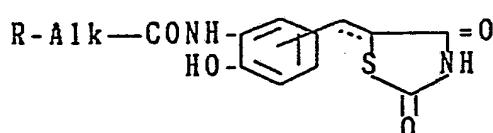


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wherein the symbol is the same as defined above, or a salt thereof,

(2) dehydrating an amide of the formula:

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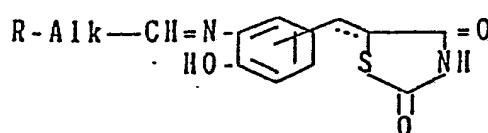


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wherein the symbols are the same as defined above, or a salt thereof or,

(3) dehydrogenating an azomethine compound of the formula:

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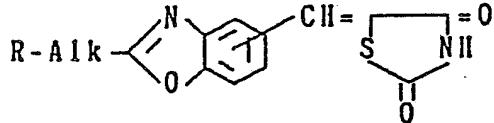
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wherein the symbols are the same as defined above, or a salt thereof, and

(4) if required, converting the product into a pharmaceutically acceptable salt thereof.

14. A process for preparing a benzoxazole derivative of the formula:

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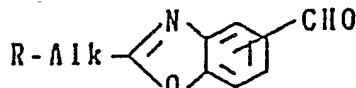
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wherein R is a substituted or unsubstituted phenyl group, a substituted or unsubstituted naphthyl group, a substituted or unsubstituted cycloalkyl group or a substituted or unsubstituted heterocyclic group; Alk is single bond, a substituted or unsubstituted lower alkylene group, a lower alkenylene group or a lower alkynylene group, or a salt thereof, which comprises the step of:

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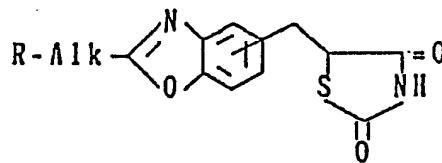
reacting the aldehyde compound of the formula:

50



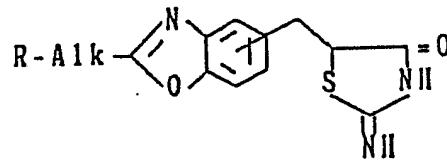
wherein the symbols are the same as defined above, or a salt thereof with 2,4-dioxothiazolidine or a salt thereof.

15. A process for preparing a benzoxazole derivative of the formula:

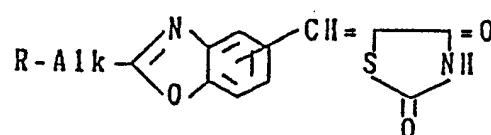


wherein R is a substituted or unsubstituted phenyl group, a substituted or unsubstituted naphthyl group, a substituted or unsubstituted cycloalkyl group or a substituted or unsubstituted heterocyclic group; Alk is a single bond, a substituted or unsubstituted lower alkylene group, a lower alkenylene group or a lower alkynylene group, or a salt thereof, which comprises the step of:

hydrolysis of an imino compound of the formula:



20 wherein the symbols are the same as defined above, or a salt thereof, or reduction of the compound of the formula:



30 wherein the symbols are the same as defined above, or a salt thereof.

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EP 88 10 4361

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
A	EP-A-0 208 420 (TAKEDA CHEMICAL INDUSTRIES LTD.) * claims 1,4,5,11-13 * ---	1,13,15 -18	C 07 D 417/06 A 61 K 31/425
A	CHEMICAL AND PHARMACEUTICAL BULLETIN, vol. 31, no. 2, 1983, pages 560-569, Tokyo, JP; T. SOHDA et al.: "Antiulcer activity of 5-Benzylthiazolidine-2,4-dione derivatives" * pages 562,563, tables I,II * -----	17	
			TECHNICAL FIELDS SEARCHED (Int. Cl.4)
			C 07 D 417/00
<p>The present search report has been drawn up for all claims</p>			
Place of search	Date of completion of the search	Examiner	
BERLIN	16-06-1988	HASS C V F	
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ..... & : member of the same patent family, corresponding document P : intermediate document	
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			